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The Vertebrate Habenula

A renowned neuroscientist, now retired from Cambridge University, once told me that he had been a graduate student in North America when he first came across the term "habenula". For him and his course mates, the habenula provided a source of humor. Nobody knew what it did, but the word sounded unusual and provoked a lot of laughter. The anatomy of habenula neurons, with their unusual terminations of loops and spirals at the midline, was a source of wonderment. There was nothing else like it in the vertebrate brain.

Now, many decades later, the habenula has become more familiar to neuroscientists. It has been implicated in psychiatric disorders such as depression, addiction and schizophrenia. It has roles in learning and aggression. This multiplicity of function echoes earlier animal work, which showed that the habenula was involved in phenomenon ranging from sleep, to maternal care and ability to perform in stressful situations. The difference is that now we have a better understanding of how the habenula can influence so many aspects of behavior.

A major function of the habenula is to regulate neuromodulators. The most widely known of these are dopamine and serotonin, but the habenula can also control other broadly acting modulators, such relaxin-3 from the nucleus incertus. Given this, one way of understanding the function of the habenula is to think in terms of modes, a term use by Getting to describe patterns of network connectivity.

Neurons are wired to one another during development and these connections are modified during learning to form an anatomical network. However, functional connectivity, which determines behavior, can be altered dynamically – on very short timescales - by neuromodulators. These act at synapses to control the effective architecture of the nervous system. One consequence of this is that the brain contains a multitude of functional connectomes, i.e. multiple modes. Because the habenula receives input about the external environment, from apparently all sensory systems, and about the internal environment, e.g. time of day and nutritional level, the habenula provides a way for the functional connectome to be linked to the needs of the animal.

This issue aims to introduce the habenula to cell and developmental biologists, with the idea that there are still many opportunities for discoveries within this system. Developmental biologists may already have some familiarity with the habenula, as it has been well studied from the perspective of asymmetry, especially in lower vertebrates. There are other intriguing aspects, such as the formation of connections in the interpeduncular nucleus. Here, growing axons cross the midline multiple times, very much in contrast to commissural axons in the rest of the brain or spinal cord. Their behavior is reminiscent of the *roundabout* mutant in *Drosophila*, raising the question of whether there is natural loss of a similar guidance pathway here. Other developmental questions include how the diversity of cell types within the habenula, especially within the lateral habenula, is generated. Formation of the habenula commissure also has some interesting features, including a constant release of what appear to be exomes, from the tips of crossing axons.

From the perspective of cell biologists, one potential area of interest is membrane excitability. Habenula neurons are highly active, even when the animal appears to be doing nothing, as can be readily seen in any calcium imaging study in zebrafish larvae. What mediates this activity is unknown. The spirals at axon terminals are also a mystery – how does this architecture contribute to signaling?

The articles here cover a range of biology. Sten Grillner and colleagues consider the habenula from an evolutionary perspective. As their work on the lamprey has shown, the habenula is ancient. Sara Roberson and Marnie Halpern discuss the embryonic development of the habenula, highlighting the development of the projection from the dorsal habenula to the interpeduncular nucleus, in addition to reviewing asymmetry. In the next article, I consider connectivity of the habenula, in particular reviewing an input from the thalamus, which is a major hub of the vertebrate brain. Then, Ajay Mathuru presents a comprehensive review of the role of the habenula in reward processing. Finally, Stephanie Fore et al provide a computational perspective on the habenula, asking the question of how the habenula is able to process information from diverse sources to provide a coherent output to neuromodulatory and other downstream systems.

Together, these articles provide a complementary dimension to the growing body of literature on the habenula, and help elicit wonderment and excitement in this generation of graduate students.

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